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Diels-Alder Reactions of 2-Alkenylboranes and *cis*-1-Alkenylboranes. Anomalous Selectivity that Allows a Choice of Regiochemistry

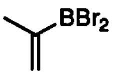
Daniel A. Singleton,* Kyeongsook Kim, and Jose P. Martinez

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Abstract: 2-Alkenyl- and *cis*-1-alkenylboranes are highly reactive Diels-Alder dienophiles which display unusual selectivity patterns. By taking advantage of a reversal of regiochemistry of reactions with alkenyldihalo- versus alkenyldialkylboranes, any desired regioisomeric product may be favored, usually with very high selectivity.

In 1972 Coindard and Braun reported that vinyldihaloboranes were reactive Diels-Alder dienophiles.[1] Unfortunately, these dienophiles have exhibited only poor selectivity. Coindard and Braun observed a 1:1 mixture of endo and exo products with cyclopentadiene. In a recent study of vinyldihalo- and *trans*-alkenyldihaloboranes, the best regioselectivity was 70:30 and the best stereoselectivity was 55:45.[2] Our initial observation of low selectivity and inconsistent yields with vinyldihaloboranes[3] caused us to favor the much more selective vinyldialkylboranes.[3,4] In contrast to these discouraging results, we report here that 2-alkenyl- and *cis*-1-alkenyldibromoboranes are highly regioselective dienophiles. We also report that the first examples of Diels-Alder reactions of 2-alkenyl- and *cis*-1-alkenylboranes exhibit unusual regio- and stereoselectivity patterns. This includes an intriguing reversal in the favored regioisomer with alkenyldihaloboranes versus alkenyldialkylboranes, which both allows a rare[5] choice of product regiochemistry for Diels-Alder reactions and suggests the importance of a novel stereoelectronic effect.

The alkenylboranes **1-6** were readily generated in situ[6] from the reaction of BBr_3, BCl_3, 9-bromo-BBN, or *B*-chloro-3,6-dimethylborepane[7] with 2-propenyltributyltin or *cis*-1-propenyltributyltin. A 1.3-fold excess of the alkenyltributyltin was used to remove adventitious protic acid; this particularly improves the consistency of yields with the alkenyldihaloboranes. NMR studies indicate that the formation of **1**, **2**, **5**, and **6** occurs quickly and quantitatively at 0 °C. The formation of **3** and **4** requires heating to 55 °C, which was generally carried out in the presence of the diene.



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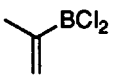

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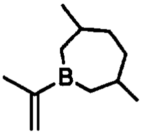

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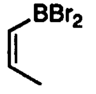

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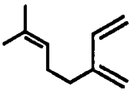
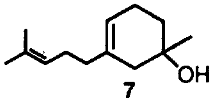
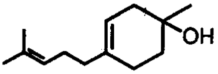
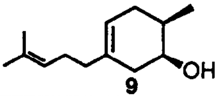
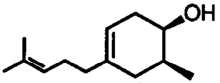
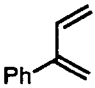
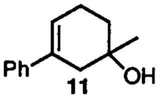
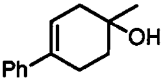
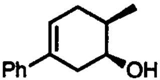
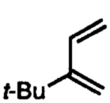
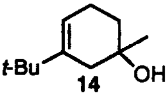
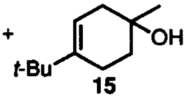
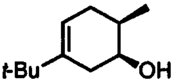
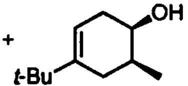
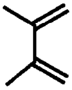
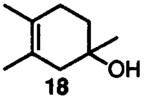
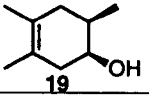
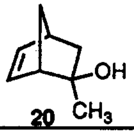
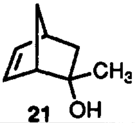
The reactivity and selectivity of the alkenylboranes were surveyed in reactions with several dienes (Table 1).[8] The relative reactivity of 2-propenylboranes was **1** > **2** > **3** $\approx$ **4**; **1** reacts rapidly with simple dienes at room temperature, while **3** and **4** requires longer reaction times at 55 °C. The order of reactivity of alkenyldibromoboranes is **1** > **5** > *trans*-1-propenyl. The latter rate difference allows the use of stereochemically impure 1-propenyltin – when an 88:12 mixture of *cis*- and *trans*-1-propenyltributyltin was used in a reaction with 0.67 equivalents of myrcene, < 4% of the *trans*-substituted product was detected.

Table 1. Reaction Conditions, Products, and Yields for Diels-Alder Reactions of Alkenylboranes.

Diene	Alkenyl-borane	Reaction Conditions[a]	Yield[b] (Ratio)	Product(s)
	1	25 °C, 3 h	77% (100:0)	 7 +  8
	2	25 °C, 22 h	74% (80:20)	
	3	55 °C, 30 h	68% (10:90)	
	5	25 °C, 24 h	75% (100:0)	 9 +  10
	6	90 °C, 4 d	55% (31:69)	
	1	25 °C, 2 h	90% (87:13)	 11 +  12
	5	25 °C, 24 h	90% (100:0)	 13
	1	25 °C, 4.5 h	77% (68:32)	 14 +  15
	3	55 °C, 12 h	72% (0:100)	
	4	55 °C, 5 d	72% (14:86)	
	5	25 °C, 24 h	74% (90:10)	 16 +  17
	6	45 °C, 3 d	33%[c] (24:76)	
	1	25 °C, 4 h	75%	 18
	5	25 °C, 24 h	80%	 19
	3	55 °C, 2 d	70% (93:7)[d]	 20 +  21

[a] See ref 8 for an example procedure. [b] All yields refer to isolated materials after purification by flash chromatography. [c] This reaction was not taken to completion. [d] For the stereochemical assignment, see ref 1.

When pure *cis*-1-propenyltributyltin was used, *cis*-substituted products[9] were formed exclusively. This indicates that both the boron-tin exchange in the formation of *cis*-1-propenylboranes and the subsequent Diels-Alder occur with complete retention of configuration.

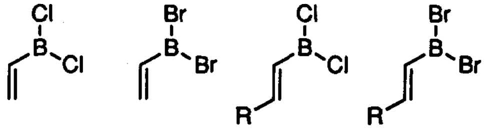
The regiochemistry of 7-17 were assigned from a combination of ^{1}H NMR decoupling studies and chemical conversions: the alcohols could be dehydrated with mesyl chloride/triethylamine followed by treatment the resulting diene with DDQ to afford the readily-assignable aromatic products. The direct assignment of **7**-**17** by ^{1}H NMR is complicated by coupling of the vinylic protons with both the vicinal and allylic methylene protons. However, the regiochemistry of **9** and **11** could be assigned from decoupling experiments based on the observation in each that the vinylic proton exhibited larger (vicinal) couplings ($\approx$ 4 Hz) with the methylene protons vicinal to the hydroxyl group, and exhibited smaller (allylic) coupling constants of $\approx$ 2 Hz with the other methylene protons.[10]

The most striking observation in Table 1 is that the alkenyldihalo- and alkenyldialkylboranes consistently favor regiochemically-reversed products. In each case, the alkenyldihaloboranes afforded the unusual "meta" (1,3) as major products, while the alkenyldialkylboranes afforded the normal "para" (1,4) as major products. The regioselectivities of **3** and **5** were consistently outstanding (90:10 in the worst case). The reaction of **1** with myrcene was regiospecific, but the selectivity decreased somewhat with larger diene substituents. Dienophiles **2**, **4**, and **6** were less selective. Importantly, by correct choice of alkenylborane very high selectivity for most of the possible regioisomeric products can be obtained.

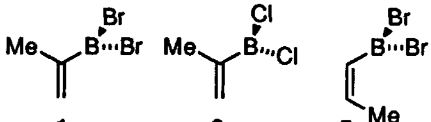
Like the parent vinyldialkylboranes,[4c] the regioselectivity with **3** and **4** appears to be steric in origin, as indicated by the greater selectivity with 2-*tert*-butylbutadiene over myrcene, and with the bulky **3** over **4**. This steric control of regioselectivity is consistent with ab initio calculations which predict a [4+3] transition state for these reactions with negligible charge buildup, but with a close approach of the alkyl groups on boron to the diene.[11]

The unusual meta regiochemistry with alkenyldihaloboranes is more difficult to explain. If this preference for the meta products were due to some unknown steric factor, enhanced selectivity for the meta product would be expected in the reaction of **1** with 2-*tert*-butylbutadiene over that with myrcene. Instead, the selectivity drops from 100:0 to 68:32.

The unusual regiochemistry seems related to the nonplanarity of 2-alkenyl- and *cis*-1-alkenyldihaloboranes. MNDO calculations predict that vinyldichloroborane, vinyldibromoborane, *trans*-1-propenyldichloroborane, and *trans*-1-propenyldibromoborane should all have essentially planar structures. The Diels-Alder reactions of each afford normal (although moderate) para regioselectivity. In contrast, MNDO calculations predict highly nonplanar structures (twisted 65-79° about the C–B bond) for **1**, **2**, and **5**. It is also notable that the barrier to planarity in the less-selective **2** is lower than that in **1** (1.3 vs 1.7 kcal).



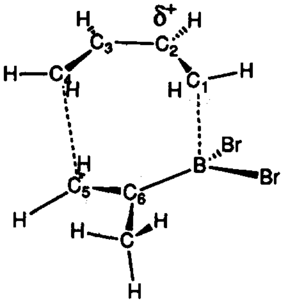
planar, give moderate normal regioselectivity



1 **2** **5**

twisted, give reversed regioselectivity

Twisting of the C–BX$_2$ bond away from planarity effectively localizes the LUMO on boron. Based on our recent theoretical and experimental studies on acetylenic boranes,[12] we envision that this localization of the LUMO results in a [4+3] transition state that looks something like **22**, in which there is advanced bonding of B to C$_1$ relative to the bonding of C$_5$ to C$_4$. This would result in a partial positive charge buildup on C$_2$, which would account for the observed regiochemistry.



22

The high *exo* stereoselectivity in the reaction of **3** with cyclopentadiene is also surprising, since vinyldialkylboranes are highly endo selective.[3,4c] A possible explanation is that a [4+3] transition state leading to the endo product would be disfavored by a steric interaction of the cyclopentadiene methylene group with the methyl group of 3. However, further work is clearly needed to more carefully define the origin of both stereo- and regioselectivity in Diels-Alder reactions of borane-activated dienophiles.

At this point, it is clear that these reactions do not follow the usual rules for selectivity in Diels-Alder reactions, but the anomalous behavior does present synthetic opportunities. The high reactivity and selectivity of 2-alkenyl- and *cis*-1-alkenylboranes, along with the ability to control their regioselectivity, should broaden the utility of boron-activated dienophiles. We are continuing to study these synthetically useful and physically intriguing reactions.

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7. Brown, H. C.; Zaidlewicz, M. *J. Am. Chem. Soc.* **1976**, *98*, 4917.
8. In a typical procedure, 3.0 mL (2.0 mmol) of a 1.0 M solution of BBr_3 in hexanes was cooled to 0 °C, and 1.32 g (4.0 mmol) of 2-propenyltributyltin was added. After 30 min at 0 °C, the mixture was allowed to warm to 25 °C, and 272 mg (2.00 mmol) of myrcene was added. The resulting mixture was stirred for 3 h, then was cooled to 0 °C, and treated with 10 mL of THF, 5 mL of 3 N NaOH, and (CAUTION: slowly) 5 mL of 30% H_2O_2, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was then extracted with three 20-mL portions of 1:1 ether/petroleum ether, and the combined organic layers were rinsed with 20 mL of brine, dried (Na_2SO_4), and the solvent was removed on a rotary evaporator. The residue was chromatographed on a 14-in. X 19-mm silica gel column using 13% EtOAc/petroleum ether as eluent to afford 300 mg (77%) of **7** as a clear liquid.
9. The cis stereochemistry was assigned from the coupling patterns of the carbinyl protons, which in each case exhibited no coupling constants >6 Hz, indicative of an equatorial carbinyl proton (axial hydroxyl group).
10. We urge caution in assumptions about the regiochemistry of products from vinylborane Diels-Alder reactions.
11. Singleton, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 6563.
12. Singleton, D. A.; Leung, S. -W. *J. Org. Chem.* **1992**, *57*, 4796. Acetylenic boranes are the only other dienophiles which electronically favor formation of the unusual meta product. In acetylenic boranes, there is a relatively large LUMO coefficient on boron, and ab initio calculations predict a transition state similar to that depicted in **22**.

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